and filing date. For the Examiner's convenience, a copy of the new declaration is enclosed.

II. CLAIM AMENDMENTS

Claims 10 and 29-53 are now pending. Newly added claims 29-53 are supported throughout the specification and by the original claims. Examples of such support are located at:

Claim(s)	Support Example(s)
29	page 6, line 28 to page 7, line 9; page 7, lines 18-24
30, 43	claim 14
31	page 26, lines 9-25; page 27, lines 11-17
32	claim 10; page 29, line 6- page 31, line 29
33, 36	page 29, lines 25-28; page 34, lines 12-17
34	page 29, line 27 – page 30, line 10; page 36, lines 3-7
35	claim 10; page 27, lines 18-23
37	page 29, lines 27-28
38	page 55, lines 13-24
39	page 55, lines 13-24
40	claims 10 and 11
41, 45	claim 12
42	page 7, lines 26-28
44	claims 10 and 16
46	claim 17
47	claim 18
48	page 16, line 23 - page 17, line 2; page 26, line 29 - page 27, line 4; page 45, line 15 – page 46, line 10
49	claim 16; page 27, lines 19-21
50, 51	page 44, lines 24-29
52	claims 10 and 19; page 8, lines 1-7
53	claim 20

No new matter has been added by these amendments. Reconsideration of the application is respectfully requested.

III. ENABLEMENT

Claim 10 was rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not "provide enablement for method wherein the activity of a compound is first tested for modulating the activity of PKCε by any and all methods and then it's activity is tested for anti anxiety effects in any and all subjects." Paper number 7, page 3, lines 1-3. The methods and subjects are addressed separately below.

A. Methods for Determining Modulation of PKCε Activity

This enablement rejection was summarized in the Official Action as "the specification does not provide sufficient disclosure about the in vivo methods of testing compounds that would have PKCε modulatory activity." Paper number 7, page 4, lines 28-30.

Applicant submits that the enablement requirement of 35 U.S.C. §112, first paragraph, has been satisfied because the specification plus known assays and established experimental techniques provide sufficient guidance to allow one skilled in the art be to use the claimed invention without undue experimentation.

The pending enablement rejection appears to be based upon a misunderstanding of claim 10. Claim 10 does not include a step for measuring a test compound's modulation of PKCε activity. Rather it includes a step for selecting a test compound based on its ability to modulate the activity of PKCε. As such, the claimed invention could be practiced without any knowledge of how to assess PKCε activity. The ample disclosure provided in the specification regarding various acellular and cellular assays for measuring PKCε activity far exceeds that necessary to comply with the enablement requirement on this point.

Applicant also respectfully notes that the discussion of PKCε-deficient mice on page 4 of the Official Action is not relevant to the enablement of methods of determining PKCε activity modulation by test compounds because, as noted by the Examiner, these mice do not express PKCε and cannot be used to test the activity of PKCε.

Withdrawal of this enablement rejection is requested.

B. Subjects for Determining Modulation of Anxiety Symptoms

The Examiner's contention that the anxiety-testing portion of the claimed invention is not enabled in any and all subjects appears to be based on a concern that the skilled artisan would not know which animals can be used as models for anxiety. Behavioral variations between male and female PKCε knockout mice and between different inbred strains of mice were also cited as support for the enablement rejection.

Applicant respectfully submits that this aspect of claim 10, when properly understood, is enabled. The rejection appears based on two incorrect assumptions: first that the second step of claim 10 must be performed upon an accepted model for anxiety and second that anxiety differences between genetically different organisms within the same species would prevent practice of the second step on subjects from that species. Regarding the model system assumption, the second step of claim 10 need not be performed on an organism that displays persistent or enhanced anxiety. Rather, it can be performed on any organism that displays reproducible symptoms of anxiety under the test conditions. Since the vast majority of animals (including humans) are known to display anxiety symptoms in response to characterized stimuli, one of skill in the art would know how to cause anxiety and monitor its modulation by a test compound in a sufficient number of subjects for claim 10 to satisfy the enablement requirement.

With respect to the assumption based upon anxiety differences, PKCε-deficient mice cannot be used to determine whether test compounds that modulate PKCε affect anxiety because the mice lack PKCε and will be unaffected by such modulators. The strain-specific behaviors described by Rogers et al, *Behavioral Brain Research* **105**: 20-217, 1999, also do not preclude enablement because one of skill in the art would know that test compound-induced modulation of anxiety symptoms can be reliably determined by comparing the symptoms of the same animal with and without the test compound or by comparing the symptoms of two or more animals that display substantially similar anxiety symptoms in the absence of the test compound, where some but not all of the animals have received the test compound.

For the reasons described in the preceding sections, the Applicant respectfully requests withdrawal of the rejection of claim 10, under 35 U.S.C. §112, first paragraph.

II. DEFINITENESS

A. Essential Steps

Claim 10 was rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps. Section 2172.01 of the MPEP was cited as support for this rejection but it indicates that the proper rejection would be either an *enablement* rejection for omission of essential steps or a *definiteness* rejection for failure to interrelate essential elements. Although Applicant is not clear which rejection was intended, Applicant respectfully submits that claim 10 neither omits essential steps nor fails to interrelate essential elements and the rejection should therefore be withdrawn.

The Official Action lists the following as allegedly omitted steps: "how is the modulation of PKCε activity by a test compound monitored, is the modulation of PKCε activity tested in vitro or in vivo, how is it determined that a test compound modulates the symptoms of anxiety or what are the symptoms of anxiety that are monitored." Paper number 7, page 6, lines 3-6. With all due respect, none of these items is an essential step for claim 10 and none of these items provides interrelation of essential elements of claim 10. Rather, the amendment of claim 10 to add the first item would add a step that is not essential to claim 10 because the test compound's ability to modulate PKCε activity may be known or may be determined prior to the performance of the claim method.

The addition to claim 10 of the other items listed in the previous paragraph would not add or interrelate essential steps, but would limit the scope of the existing steps of the claim. This distinction was recognized in a case cited in MPEP § 2172.01, *In re Mayhew*, 527 F.2d 1229, 1233 (C.C.P.A. 1976). The invention in *In re Mayhew* was a method for producing an iron-zinc coating. Some claims omitted an essential cooling bath step, while others included the step, but failed to provide a precise temperature. The Court of Customs and Patent Appeals held that the claims that excluded the cooling bath step were not enabled, for having omitted an essential step. The claims that included the bath, but not the temperature were allowed. This case is similar. While claim 10 does not specify the method(s) by which modulation of the symptoms of anxiety might be monitored, the

claim 10 does include the step in which the modulation determination is made. Withdrawal of this rejection is therefore proper.

B. "Subject"

Claim 10 was also rejected under 35 U.S.C. §112, second paragraph, as vague and indefinite because the meaning of the term "subject" was alleged to be unclear.

Applicant respectfully submits that one skilled in the art would understand the word "subject" to mean "a person or animal which has been the object of treatment, observation, or experiment." Dorland's Medical Dictionary (27th Ed. 1988). This meaning is unambiguous and withdrawal of the indefiniteness rejection is requested.

III. NONOBVIOUSNESS

Claim 10 was rejected under 35 U.S.C. §103(a) as obvious over Salzman et al., *Harv. Rev. Psychiatry* **1**: 197-206, 1993 ("Salzman") in view of Berg et al., *Molecular Pharmacology* **45**: 826-836, 1994 ("Berg") and Stenzel-Poore et al., *J. Neuroscience* **14**: 2579-2584, 1994 ("Stenzel-Poore"). The reasoning underlying this rejection is not entirely clear to Applicant but appears to be based on the belief that Salzman teaches that drugs that affect 5-HT receptors have anxiolytic properties, that Berg supposedly demonstrates a role for PKCε in facilitating the activated 5-HT receptor's ability to cause an accumulation of cAMP, and that Stenzel-Poore presents a transgenic mouse that displays anxiety and may be used to test potential anxiolytic compounds.

It is well established that the Examiner has the burden of establishing a prima facie case of nonobviousness for each claim rejected under 35 U.S.C. §103(a) and that there are three elements of such a prima facie case: 1) a motivation to modify the references or combine the teachings; 2) a reasonable expectation of success; and 3) the reference(s) must teach or suggest all the claim limitations. With all due respect, Applicant submits that no prima facie case has been established for claim 10.

The method of claim 10 involves the selection of a test compound that modulates the activity of PKCε and the administration of this test compound to a subject to determine if symptoms of anxiety are modulated. The link between modulation of PKCε activity and anxiety is crucial to claim 10, but the combination of the cited references

fails to make this connection. Neither Salzman nor Stenzel-Poore makes any mention of PKCε. Only Berg mentions PKCε at all.

The description of Berg in the Official Action emphasizes that PKCε is present in cells treated with PMA (which depletes levels of several other isoforms of PKC) and the 5-HT_{2A} receptor still causes cAMP amplification in these cells. While this description gives the impression that PKCε is responsible for mediating the 5-HT_{2A}-dependent cAMP amplification, the authors of Berg actually reached the opposite conclusion. They interpreted these data as demonstrating that the 5-HT_{2A} receptor works by a calcium/calmodulin pathway that is independent from the PKC pathway: "the effect of 5-HT is not due to the activation of PKC isoforms that remain after long term treatment with phorbol ester, because these isoforms are known to be Ca^{+2} independent and the PKC inhibitor staurosporine, at concentrations that completely block PKC activity *in vitro* (1000nM), did not affect the 5-HT-mediated amplification." Berg, p. 834, col. 2, line 56 to p. 835, col. 1, line 2.

The Berg authors do conclude that the 5-HT_{2A} receptor also enhances cAMP accumulation through a PKC-dependent pathway. However, the PKC isoform that they believe to be responsible for this function is PKCα, not PKCε: "Because the PKC-δ and PKC-ε isoforms are sensitive to activation by phorbol ester but amplification by PMA of cAMP was completely abolished, these isoforms are unlikely to mediate the amplifying effects of 5-HT after long term PMA treatment. These findings suggest that the PKC-dependent amplification in A1A1 cells is likely mediated by PKC-α." Berg, p.834, col. 2, lines 19-25.

Since a careful reading of Berg shows no relation between PKCε and the 5-HT receptor, no combination of the cited references links PKCε and anxiety. As such, the references do not teach all of the elements of claim 10 and no prima facie case of obviousness has been presented. Furthermore, Berg teaches away from the claimed invention by concluding that PKCε is not involved in 5-HT_{2A} receptor-mediated signal transduction.

In view of the above, Applicant submits that claim 10 would not have been obvious to one of skill in the art who has read the cited references. Withdrawal of the obviousness rejection based on these references is respectfully requested.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 843-5081.

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Respectfully submitted,
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